57. (Previously presented) The method of claim 50, wherein the tumor is a sarcoma.

58. (Previously presented) The method of claim 51, wherein the toxin is Pseudomonas exotoxin.

59. (Currently amended) The method of claim ~~51~~ 52, wherein the tumor suppressor protein is apoptin.

60. (Previously presented) The method of claim -53, wherein the cytokine is IL-12.

61. (Previously presented) The method of claim 51, wherein delivery of the serum-stable nucleic acid-lipid particle is intravenous.

REMARKS

The Invention

The present invention is directed to methods of treating a tumor in a mammal involving delivering to the tumor a serum-stable nucleic acid-lipid particle comprising a nucleic acid portion that is fully encapsulated within the lipid portion. Delivery of the nucleic acid-lipid particle is by injection at a site distal to the tumor in the mammal. The lipid portion of the nucleic acid-lipid particle comprises a cationic lipid, a neutral lipid, a lipid conjugate that prevents aggregation during formulation. In some embodiments, a prodrug is also administered to the mammal. In other embodiments, a chemotherapeutic agent is also administered to the mammal. In some embodiments, delivery of the nucleic acid-lipid particle is intravenous.

Status of the Claims

After entry of this amendment, claims 1-35, 37-41, and 43-61 are pending. Claims 1, 4, 7, 15, 22, 26, 28, 37, 38, and 59 have been amended to clarify the scope of the claims, to correct antecedent basis, and to ensure proper claim dependency. More particularly, claim 1 has been amended to recite that "said cells of said tumor are responsive to said nucleic

acid" and "said cells of said tumor are transfectable by said nucleic acid." Claim 4 has been amended solely for clarity to recite "heterologous to a gene in the mammal." Claim 7 has been amended solely for clarity to recite "homologous to a gene in the mammal." Claim 15 has been amended solely for clarity to recite "that of PEG-Cer20." Claim 22 has been amended to recite "the nucleic acid particles" to ensure correct antecedent basis. Claim 26 has been amended solely for clarity to recite "*in vitro.*" Claim 28 has been amended to recite "delivering" to ensure correct antecedent basis. Claims 37 and 38 have been amended to depend on pending claim 35 rather than canceled claim 36. Claim 59 has been amended to depend on claim 52 to ensure correct antecedent basis. Support for these amendments is found throughout the specification and claims as filed.

Claims 1-12, 14-35, 37-41, and 43-61 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite; claims 1-12, 14-35, 37-41, and 43-61 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement; claims 1-5, 7, 8, 10-12, 14-26, 28, 43-49, and 53 stand rejected under 35 U.S.C. §102(e) as allegedly anticipated; and claims 1, 2, 5, 6, 9, 27, 35, 37-41, 47, and 50-61 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable. These rejections are addressed below, in the order presented by the Examiner.

Rejections Under 35 U.S.C. §112, second paragraph

Claims 1-12, ,14-35, 37-41, and 43-61 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants respectfully traverse this rejection.

> As set forth in MPEP § 2173.02, "[d]efiniteness of claim language, must be analyzed in light of (A) content of the application; (B) the teachings of the prior art; and (C) the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made."

In the instant case, the specification adequately defines the terms or the terms are adequately understood to one of skill in the art, such that the claims are not indefinite under 35 U.S.C. §112, second paragraph. Several bases of indefiniteness were raised, and they will be discussed in turn.

1. Claims 1, 47, and 48

Claims 1, 47, and 48 have been rejected under 35 U.S.C. §112, second paragraph, as allegedly unclear for the recitations "treating a tumor," "wherein the tumor is responsive to a gene product," and "wherein cells of a tumor are transfectable." Applicants respectfully submit that one of skill in the art would understand each of the recitations. Moreover, the specification defines each of these claim terms such that one of skill in the art could easily determine their meaning.

The specification at, *e.g.*, page 19, lines 30-32 describes treatment as a therapeutic effect at the site of a neoplasia (*e.g.*, a tumor). In addition, as set forth in the specification at page 7, lines 18-25, a therapeutic effect for a neoplasia (*e.g.*, a tumor) includes, "a reduction in growth, inhibition, or reduction in the size of the neoplasia or inhibition or reduction of metastasis." Finally, the specification at page 9, line 26 to page 10, line 11 explains that transfection comprises introducing nucleic acids into cells. Accordingly, Applicants respectfully submit that each of the recitations is easily understood by one of skill in the art and request withdrawal of this aspect of the rejection under 35 U.S.C. §112, second paragraph.

2. Claim 2

Claim 2 has been rejected under 35 U.S.C. §112, second paragraph, for allegedly lacking antecedent basis for the recitation "said nucleic acid." Applicants respectfully submit that the recitation "said nucleic acid" finds support in claim 1, line 3 which recites, *inter alia*, "a nucleic acid." Accordingly, Applicants respectfully request withdrawal of this aspect of the rejection under 35 U.S.C. §112, second paragraph.

3. Claim 4

Claim 4 has been rejected under 35 U.S.C. §112, second paragraph, as allegedly unclear for the recitation "heterologous." In accordance with the Examiner's suggestions, claim 4 has been amended to recite "heterologous to a gene in the mammal." Accordingly, Applicants respectfully request withdrawal of this aspect of the rejection under 35 U.S.C. §112, second paragraph.

4. Claim 7

Claim 7 has been rejected under 35 U.S.C. §112, second paragraph, as allegedly unclear for the recitation "homologous." In accordance with the Examiner's suggestions, claim 4 has been amended to recite "homologous to a gene in the mammal." Accordingly, Applicants respectfully request withdrawal of this aspect of the rejection under 35 U.S.C. §112, second paragraph.

5. Claim 10

Claim 10 has been rejected under 35 U.S.C. §112, second paragraph, as allegedly unclear for the recitation "therapeutically effective amount of said gene is generated at said tumor." As set forth in the specification at page 7, lines 18-19, a therapeutically effective amount is an amount that is sufficient to give rise to a desired therapeutic effect. Moreover, as explained in the specification at page 10, lines 15-21, therapeutic nucleic acids may encode polypeptides or polynucleotides. Thus, based on the teachings in the specification, one of skill in the art would appreciate that a therapeutically effective amount of the polypeptide or polynucleotide encoded by the nucleic acid would be generated at the tumor. Accordingly, Applicants respectfully request withdrawal of this aspect of the rejection under 35 U.S.C. §112, second paragraph.

6. Claim 15

Claim 15 has been rejected under 35 U.S.C. §112, second paragraph, as allegedly unclear for the recitation "at a rate faster than PEG-Cer20." In accordance with the Examiner's

suggestion, claim 15 has been amended to recite "at a rate faster than that of PEG-Cer20." Accordingly, Applicants respectfully request withdrawal of this aspect of the rejection under 35 U.S.C. §112, second paragraph.

7. Claim 22

Claim 22 has been rejected under 35 U.S.C. §112, second paragraph, as allegedly unclear for the recitation "said nucleic acid particles." In accordance with the Examiner's suggestion, claim 22 has been amended to recite "the nucleic acid particles." Accordingly, Applicants respectfully request withdrawal of this aspect of the rejection under 35 U.S.C. §112, second paragraph.

8. Claim 26

Claim 26 has been rejected under 35 U.S.C. §112, second paragraph, because it is allegedly unclear whether the limitation that the nucleic acid remains at least 90% intact upon treatment with DNAse is a further limitation on claim 1. Applicants respectfully point out that claim 1 contains no limitation on or reference to the percentage of nucleic acid that remains intact. Accordingly, dependent claim 26 does introduce a further limitation on claim 1. The Examiner further alleges that it is unclear how the DNAse treatment could be performed *in vivo*. In accordance with the Examiner's suggestion, claim 26 has been amended to recite "DNA is treated *in vitro*." Accordingly, Applicants respectfully request withdrawal of this aspect of the rejection under 35 U.S.C. §112, second paragraph.

9. Claim 28

Claim 28 has been rejected under 35 U.S.C. §112, second paragraph, as allegedly unclear for the recitation "said administering." To ensure correct antecedent basis, claim 28 has been amended to recite "said delivering." Accordingly, Applicants respectfully request withdrawal of this aspect of the rejection under 35 U.S.C. §112, second paragraph.

10. Claims 37 and 38

Claims 37 and 38 have been rejected under 35 U.S.C. §112, second paragraph, as dependent on a canceled claim, *i.e.*, claim 36. To ensure correct dependency, claims 37 and 38 have been amended to depend on claim 35, which is pending. Accordingly, Applicants respectfully request withdrawal of this aspect of the rejection under 35 U.S.C. §112, second paragraph.

11. Claim 59

Claim 59 has been rejected under 35 U.S.C. §112, second paragraph, as lacking antecedent basis for the recitation "the tumor suppressor protein." Claim 59 has been amended to depend on claim 52, which recites "a tumor suppressor protein." Accordingly, Applicants respectfully request withdrawal of this aspect of the rejection under 35 U.S.C. §112, second paragraph.

Rejections Under 35 U.S.C. §112, first paragraph

Claims 1-12, ,14-35, 37-41, and 43-61 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement. In making this rejection, the Examiner acknowledges that the claims are fully enabled for method of treating a tumor by delivering a nucleic acid-lipid particle where the tumor is responsive to the nucleic acid or where the tumor cells are transfectable by the nucleic acid, but alleges that the claims are not enabled for a method of treating a tumor by delivering a nucleic acid-lipid particle where the tumor is not responsive to the nucleic acid or where the tumor cells are not transfectable by the nucleic acid.

A particular claim is enabled by the disclosure in an application if the disclosure, at the time of filing, contains sufficient information so as to enable one of skill in the art to make and use the claimed invention without ***undue*** experimentation. *See, e.g., In re Wands*, 8 USPQ2d, 1400 (Fed. Cir. 1988), or MPEP §2164.01. Moreover, as set forth in MPEP § 2164.08, a rejection for undue breadth is inappropriate where "one of skill could readily determine any one of the claimed embodiments."

As acknowledged by the Examiner the claims are fully enabled for methods of treating a tumor by delivering a nucleic acid-lipid particle where the tumor is responsive to the nucleic acid or where the cells of the tumor are transfectable by the nucleic acid. Thus, one of skill in the art could readily determine any one of the claimed embodiments, and, therefore, the claims are fully enabled for methods of treating a tumor by delivering nucleic acid-lipid particles. However, to expedite prosecution, Applicants have amended the claims in accordance with the Examiner's suggestion to recite that the "cells of said tumor are responsive to said nucleic acid" and that the "cells of said tumor are tranfectable by said nucleic acid."

In view of the foregoing remarks, Applicants assert that claims are fully enabled by the specification as originally filed and respectfully request that the enablement rejection under 35 U.S.C. § 112, first paragraph, be withdrawn.

Rejections Under 35 U.S.C. § 102(e)

Claims 1-5, 7, 8, 10-12, 14-26, 28, 43-49, and 53 stand rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Semple *et al.* (U.S. Patent No. 6,287,591). Applicants respectfully traverse this rejection.

For a rejection of claims under § 102(e) to be properly founded, the Examiner must establish that a single prior art reference discloses each and every element of the claimed invention. *See, e.g.* , *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q. 81 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987). In *Scripps Clinic & Research Found. v. Genentech, Inc.*, 18 U.S.P.Q.2d 1001 (Fed. Cir. 1991), the Federal Circuit held:

> [A]nticipation requires that all of the elements and limitations of the claim are found with a single prior art reference. . . .There must be ***no difference*** between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. *Id.* at 1010 (emphasis added).

Anticipation can be found, therefore, only when a cited reference discloses ***all*** of the elements, features or limitations of the presently claimed invention.

As explained above, the present invention relates to methods of treating a tumor in a mammal by delivering to the mammal a serum-stable nucleic acid-lipid particle comprising a

nucleic acid portion that is fully encapsulated within the lipid portion. Delivery of the nucleic acid-lipid particle is by injection at a site distal to the tumor in the mammal.

Semple *et al.* is cited by the Examiner as disclosing treating a tumor in a mammal by distal administration of a nucleic acid-lipid particle. As explained in the Declaration of Dr. Ian MacLachlan, Semple *et al.* is not prior art and does not anticipate the presently claimed invention. More particularly, the relevant disclosures of Semple *et al.* have a priority date that is after the date that the invention disclosed and claimed in the present application was first disclosed (*see, e.g.*, Declaration ¶ 5). Semple *et al.* issued from U.S. Patent Application No. 09/078,954, filed May 14, 1998 which was a continuation-in-part of U.S. Patent Application No. 08/856,374 filed May 14, 1997 (*see*, Declaration ¶ 6). As explained by Dr. MacLachlan, disclosure of relating to treatment of tumors by any method, including by delivery of nucleic acid-lipid particles by injection at a site distal to the tumors was added to the continuation-in-part application filed May 14, 1998 (*see*, Declaration ¶6). Therefore, the earliest priority date of the relevant disclosure of Semple *et al.* is May 14, 1998, well after February 3, 1998, the priority date of the present application. Moreover, as explained by Dr. MacLachlan, U.S. Patent Application No. 60/072,598, filed February 2, 1998, which is the earliest priority document for the present application, discloses methods of treating tumors in mammals by delivering nucleic acid-lipid particles to a site distal from the tumor (*see*, Declaration ¶ 7). Accordingly, the relevant disclosures of Semple *et al.* have a priority date (May 14, 1998) that is ***after*** the disclosure of the presently claimed methods of treating tumors and Semple *et al.* is not available as prior art against the presently claimed invention.

In view of the foregoing, Applicants respectfully submit that Semple *et al.* is not prior art and respectfully request withdrawal of the rejection under 35 U.S.C. § 102(e).

Rejections Under 35 U.S.C. § 103(a)

Claims 1, 2, 5, 6, 9, 27, 35, 37-41, 47, and 50-61 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Semple *et al.* in view of the teachings of Fulton *et al.* (U.S. Patent No. 6,506,550); Hung *et al.* (U.S. Patent No. 6,197,754); Zhuang *et al.*, *Cancer Res.*

55:486-489 (1995); and Chaudhary *et al.*, *Nature* 339:394-397 (1989). Applicants respectfully traverse this rejection.

> As set forth in M.P.E.P. § 2143, "[t]o establish a *prima facie* case of obviousness, *three* basic criteria must be met. *First*, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. *Second*, there must be a reasonable expectation of success. *Finally*, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)."

All three elements set forth above must be present in order to establish a *prima facie* case of obviousness. Applicants respectfully assert that a *prima facie* case of obviousness has not been established for at least the following reason: the cited art references do not teach or suggest all the claim limitations.

In making this rejection, the Examiner acknowledges that Semple *et al.* do not teach administration of an expressible gene encoding HSV-TK, IL-2, apoptin, *Pseudomonas* exotoxin, or treatment of sarcoma or colorectal tumors, but alleges that Fulton *et al.*, Hung *et al.*, Zhuang *et al.*, and Chaudhary *et al.* supply the absent teachings.

As explained above in conjunction with the rejection of the claims under 35 U.S.C. § 102(e0, Semple *et al.* is not prior art and does not disclose or suggest the claimed methods of treating of tumors by delivering nucleic acid-lipid particles at a site distal to the tumors prior to the earliest priority date of the present application. None of the other cited references (*i.e.*, Fulton *et al.*, Hung *et al.*, Zhuang et al, nor Chaudhary *et al.*) disclose or suggest the presently claimed methods of treating tumors. Thus, the invention is non-obvious and patentable over cited references.

Fulton *et al.* describes use of thiamin depleting agents to induce apoptosis in vertebrate cells, but does not disclose treatment of tumors by delivery of nucleic acid-lipid particles at a site distal to the tumors.

Hung *et al.* describes delivery of nucleic acid-lipid ***complexes*** comprising a therapeutic proto-oncogenic polynucleotide (*i.e.*, a mini E1A gene) to suppress tumor growth. As previously explained in the response filed June 29, 2003 and its accompanying Declaration of Dr. Mark Murray, the nucleic acid-lipid particles disclosed in Hung *et al.* are ***complexes*** of lipids with nucleic acids in which the nucleic acids are not encapsulated. Hung *et al.* describe preparation of nucleic acid-lipid complexes by mixing preformed cationic liposomes with nucleic acids to form nucleic acid-lipid complexes (see, e.g., col. 38, line 58 to col. 39, line 30). Thus, in contrast to the presently claimed invention, Hung *et al.* do not teach nucleic acids that are fully encapsulated within the lipid of the lipid-nucleic acid particle.

Zhuang *et al.* describe apoptin induced apoptosis in human osteosarcoma cells, regardless of their p53 status, but does not describe methods of treating tumors by delivering nucleic acid-lipid particles at a site distal to the tumors.

Chaudhary *et al.* describe an antibody-toxin fusion protein, *i.e.*, anti-Tac(Fv)-PE40, in which the variable region of a monoclonal antibody to a subunit of the human IL-2 receptor is linked to PE40, a modified form of Pseudomonas exotoxin and its selective cytotoxicity to two IL-2 receptor-positive cell lines, but does not describe methods of treating tumors by delivering nucleic acid-lipid particles at a site distal to the tumors.

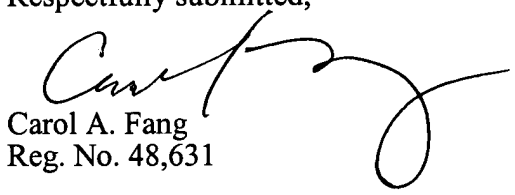
Thus, as explained above, none of the cited references disclose or suggest the claimed methods of treating tumors by delivering nucleic acid-lipid particles at a site distal to the tumor. In view of the foregoing, Applicants respectfully submit that the presently claimed invention is non-obvious and, thus patentable over the cited references and request withdrawal of the rejection under 35 U.S.C. § 103(a).

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at 415-576-0200.

Respectfully submitted,



Carol A. Fang
Reg. No. 48,631

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, 8th Floor
San Francisco, California 94111-3834
Tel: 415-576-0200
Fax: 415-576-0300
Attachments
CAF:caf
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